Lumina Indones J Neurol. Vol 2 No 2 (August 2026)
https://doi.org/10.19166/lijn.v2i2.10397

REVIEW ARTICLE

NEUROTHERAPIES FOR LONG COVID: REWIRING FATIGUE, MENTAL HEALTH, AND QUALITY OF LIFE THROUGH A SYSTEMATIC REVIEW AND NETWORK META-ANALYSIS

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Abstract

Introduction: Long COVID affects nearly 36% of post-infected individuals worldwide, many of whom experience persistent neurological symptoms such as fatigue, cognitive impairment, and mood disorders. Despite growing recognition of this condition, the most effective nonpharmacological strategies remain unclear. This study aimed to determine optimal neurotherapy to improve fatigue, mental health, and quality of life (QoL) in Long COVID patients.

Methods: A systematic review of a network meta-analysis was conducted following the PRISMA NMA guidelines. Literature searches were made using Pubmed, EBSCOhost, Wiley, and Scopus up to May 2025. Randomized controlled trials (RCT) were included with patients suffering from long COVID and treated with non-pharmacological therapy. Standard mean differences (SMD) were calculated using a frequentist approach, and treatments were ranked using the Surface under the Cumulative Ranking Curve (SUCRA). Risk of bias and certainty of evidence were assessed using the Cochrane RoB-2 and GRADE framework.

Results: Fourteen RCTs including 1,309 participants were included in the analysis. Affective and cognitive integrated therapy achieved the greatest result of decreased fatigue severity (SMD = –5.01, 95% CI –6.38 to –3.65). Multimodal therapies combining aerobic training, strength conditioning, respiratory neuroplasticity training and telerehabilitation improved QoL (SMD = 7.55, 95% CI 5.14 to 9.95). The mental health data remained insignificant due to the data being heterogeneous and publication bias.

Conclusions: Affective and Cognitive Integration and multimodal rehabilitation show potential for providing relief for fatigue and enhancing QoL in Long COVID patients. However, further standardized and longitudinal studies are needed to understand their effects on mental health.

Keywords: Long COVID, Neurorehabilitation, Fatigue, Quality of Life, Network Meta-Analysis, Non-pharmacological Therapy

Received: January 23rd, 2026
Accepted: July 10th, 2026
Published: August 10th, 2026

How to cite this paper:
Wirodiharjo MSC, Sampurno AL, Indrawan FAA, Karenina TW, Setyoko TT. Neurotherapies for long covid: rewiring fatigue, mental health, and quality of life through a systematic review and network meta-analysis. Lumina Indones J Neurol. 2026; 2(2):9-31

Introduction

Coronavirus disease 2019 (COVID-19) has affected millions of people worldwide, with the majority achieving full recovery following the acute phase of infection. However, a subset of patients continues to experience long-term effects involving multiple organ systems, including respiratory, cardiovascular, neurological, and psychological domains. This condition, referred as Long COVID, is defined as a post-SARS-CoV-2 infection syndrome characterized by new-onset symptoms occurring three months after the onset of acute infection, lasting for at least two months, and not attributable to alternative diagnoses[1]. Globally, in 2025, it is estimated that approximately 36% of COVID-19 patients are affected by this syndrome, with about 35% of cases are from Asia [2].

One of the manifestations experienced by patients with Long COVID is neurological manifestations driven by neuroinflammation[3]. According to the World Health Organization (WHO), the most reported symptoms include fatigue, shortness of breath, cognitive dysfunction, depression, and other symptoms that affect daily functioning[1]. Evidence from meta-analyses indicates a prevalence of 43.3% for fatigue, 27.1% for cognitive dysfunction, and 14% for depression[4].

There is currently no gold standard for the management of Long COVID, particularly in addressing neurological manifestations. However, evidence from the literature, especially meta-analyses, indicates that non-pharmacological interventions provide relatively strong evidence and have shown effectiveness in alleviating these symptoms[5.] On the other hand, pharmacological therapies remain limited in supporting evidence, as several studies have demonstrated non-significant results. Notably, the Food and Drug Administration (FDA) has only approved one out of four proposed drugs for the management of this condition[6,7].

Although non-pharmacological therapies are considered promising in reducing Long COVID manifestations, the interventions are highly diverse. Commonly studied approaches include aerobic exercise to alleviate fatigue, cognitive behavioral therapy (CBT) to address psychological disorders and cognitive dysfunction and breathing training to improve respiratory function and relieve dyspnea [5]. However, until now, there is no consensus or strong evidence identifying which non-pharmacological intervention is most effective. The World Health Organization (WHO) has emphasized that the current evidence regarding the effectiveness of non-pharmacological strategies in managing Long COVID remains low to moderate, highlighting the need for further well-designed studies [1].

Therefore, our study conducted a network meta-analysis to determine the most effective non-pharmacological approach for improving neurological manifestations in patients with Long COVID, by comparing three subgroups of interventions, namely rehabilitation, neuromodulation, and integrative interventions.

Materials and Methods

Study Design, Data Sources, and Search Strategies

This systematic review and network meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Network Meta-Analyses (PRISMA-NMA) guidelines which facilitated the thoroughness and trustworthiness of this review.[8] Three authors (F.A, T.T, and A.L.S.) independently and manually revisited the literature search conducted in May 2025 using four online databases, namely PubMed, EBSCOhost, Wiley, and Scopus. Supplementary Data 1 provides the basic search strategy, which had to include the use of Boolean operators "OR" and "AND" with Medical Subject Headings (MeSH) terms to carry out fairly accurate searches of the query. Every study identified was checked, according to the Universal Population, Intervention, Comparison, and Outcome (PICO) structures present in Table 1. Due to logistical constraints, this systematic review was not prospectively registered in an international database such as PROSPERO[37].

Table 1 Literature Review Inclusion Criteria Based on PICO Framework

Population	Adults diagnosed with long COVID (post-acute sequelae of SARS-CoV-2 infection) experiencing neurological or neuropsychiatric symptoms, such as fatigue, cognitive impairment, dyspnea, or mood disturbances (e.g. anxiety, depression).
Intervention	Non-pharmacological interventions grouped into: - Neuromodulation (namely, tDCS/transcranial direct current stimulation) - Rehabilitation (including Respiratory Muscle Training (RMT/IMT), Telerehabilitation Exercise (aerobic/functional/concurrent training) - Multimodal interventions (e.g. RMT + Exercise, tDCS + Exercise, or telerehab + mindfulness)
Control	Other non-pharmacological interventions, sham stimulation, usual care, or WHO guideline-based self-care.
Outcome	- Fatigue severity (pooled using SMD) - Quality of Life (pooled using SMD) - Mental health (pooled using SMD)

Selection Criteria

The studies were chosen according to pre-established inclusion and exclusion criteria to guarantee that the selected literature was relevant and high enough quality. The inclusion criteria were: (1) studies that involved adults (≥18 years) with long COVID (≥4 weeks), with or without neurological or psychiatric symptoms, (2) interventions using rehabilitation-based approaches, such as respiratory muscle training (RMT), telerehabilitation, transcranial direct current stimulation (tDCS), or multimodal **approaches**, and (3) randomized controlled trials (RCTs) that reported outcomes related to fatigue, health-related quality of life (QoL), and or mental health conditions. The exclusion criteria were: (1) studies that only provided partial or missing quantitative outcome data, (2) studies that only assessed pharmacological outcomes, and (3) studies published in a language other than English. Study selection was independently conducted by several reviewers, and disagreements were discussed until agreement was reached. Duplicate studies were then identified and removed, using citation management software, to prevent redundancy.

Data Extraction, Data Synthesis, and Assessed Outcome

After studies are filtered, data were then extracted, both qualitatively and quantitatively, from the included studies. Disagreements were resolved by discussion between the three authors (F.A, T.T, and A.L.S.), and the other authors were also consulted when necessary. We extracted qualitative data based on the following: (a) authors, (b) place or where the study had been taken, (c) study design, (d) date of publication, (e) sample size, and (f) the results of the study. Furthermore, quantitative data extraction is explained on the Statistical Analysis subtheme.

Fatigue, quality of life (QoL), and mental health outcomes were extracted using the validated assessment instruments reported in each trial. Fatigue was assessed using different instruments across studies, including the Modified Fatigue Impact Scale (MFIS), Fatigue Severity Scale (FSS), and Chalder Fatigue Scale/Questionnaire. Quality of life was evaluated using several generic and health-related QoL measures, including the SF-36, SF-12, RAND-36, EQ-5D (EuroQol-5D), and WHOQOL-BREF. Mental health outcomes were assessed using various validated instruments evaluating anxiety, depression, perceived stress, mood, or psychological wellbeing, including the Hospital Anxiety and Depression Scale (HADS), Hamilton Anxiety Rating Scale (HAM-A), Hamilton Depression Rating Scale (HAM-D), Perceived Stress Scale (PSS), and Profile of Mood States (POMS). Because these instruments use different scoring systems while assessing comparable clinical constructs, standardized mean differences (SMDs) were used to enable quantitative synthesis across studies.

Quality Appraisal

Qualities of the included Randomized Controlled Trials (RCTs) were assessed using Cochrane Risk of Bias 2.0 with the domains starting from randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result (Supplementary Data 3).[9] The assessment was done by 3 independent reviewers and presented in a traffic light plot, the outcome would range from low risk, some concerns, and high risk. All discrepancies were addressed in discussion and have reached an agreement among the reviewers. The certainty of evidence within the direct, indirect, and network estimate is conducted by GRADE Analysis, reporting studies' risk of bias, inconsistency, indirectness, imprecision, and other considerations such as publication bias that may affect the outcome (see Supplementary Data 4).[10,39]

Statistical Analysis

We used R Studio (version 4.3.1) for our analyses using netmeta and meta package.[11,12] This study conducted a network meta-analysis (NMA) to assess the comparative effectiveness of multiple interventions on the outcome. NMA was completed using a frequentist approach with both common-effects and random-effects models to calculate standardized mean differences (SMDs) and standard errors (SEs). SMDs and SEs were calculated for each study prior to the network meta-analysis from the mean difference and standard deviation data on pre and post intervention. As fatigue, quality of life, and mental health were assessed using different validated instruments across the included trials, standardized mean differences (SMDs) were selected to enable quantitative synthesis across different measurement scales. Clinical heterogeneity was anticipated because the included studies also differed in intervention characteristics, including intervention type, intensity, duration, frequency, and mode of delivery. Although SMDs reduce differences arising from scale units, conceptual differences between outcome instruments remained and were considered when interpreting pooled estimates and heterogeneity.

Frequentist NMA were conducted using the netmeta package, which generalizes the DerSimonian and Laird random-effects model to network structures which allows for full synthesis of direct and indirect evidence. 95% CIs and SMDs are presented for all pairwise comparisons. τ^2 values were used to characterize heterogeneity as noted, the global inconsistency was tested using the χ^2 test, and local inconsistency assessed using the netsplit approach comparing the direct and indirect estimates using z-tests, with $p < 0.05$ indicating significant inconsistency.

Treatment rankings were performed using visualizing the netleague table that summarizes the pairwise comparisons between interventions in matrix format and calculating the Surface Under the Cumulative Ranking Curve (SUCRA) which show the probabilistic ranking of interventions where higher SUCRA values indicated greater chance of being effective[12]. Indicators of publication bias were evaluated. The funnel plots were inspected for symmetry. A symmetrical spread of studies around the pooled effect estimate indicated a low risk of publication bias. Greater asymmetry indicated a maior bias. A trim-and-fill analysis adjusted for the effects of any potential missing studies and estimated the robustness of the overall pooled effect size with respect to missing studies.[13]

Results

Study Selection Process

The selection process of included studies is presented in the PRISMA Flow Diagram (Figure 1). A total of 1,113 records were systematically identified from four databases, comprising Scopus (n = 578), PubMed (n = 67), Wiley (n = 218), and EBSCOHost (n = 250). After removing 379 duplicate records, 734 studies remained for title and abstract screening, of which 600 were excluded. The remaining 134 reports were sought for retrieval, with 4 reports not retrieved. Subsequently, 130 full-text articles were assessed for eligibility, resulting in the exclusion of 116 studies for not reporting at least one of the outcomes of interest. Ultimately, 14 studies met the inclusion criteria and were included in the final review. Summary of the studies are presented on Supplementary Data 2.

Study and Populations Characteristic of Included Studies

A total of 1,309 participants (intervention: 657, control: 652) from the 14 selected RCTs were included (Figure 1). Participants' mean age ranged from 38.9 ± 11.1 to 67.6 ± 10.6 years. The studied populations were adults with post-acute sequelae or long COVID, presenting with fatigue, dyspnea, impaired exercise tolerance, or cognitive symptoms. The included trials originated from Brazil (n = 1), Germany (n = 1), Spain (n = 3), United Kingdom (n = 1), Egypt (n = 1), United States (n = 2), Taiwan (n = 1), England (n = 1), Italy (n = 1), Saudi Arabia (n = 1), and Canada (n = 1), published between 2022 and 2025.

Intervention categories like aerobic training (3 studies), aerobic training combined with telerehabilitation (2 studies), neuromodulatory brain stimulation (1 study), respiratory neuroplasticity training (1 study), affective and cognitive integration with

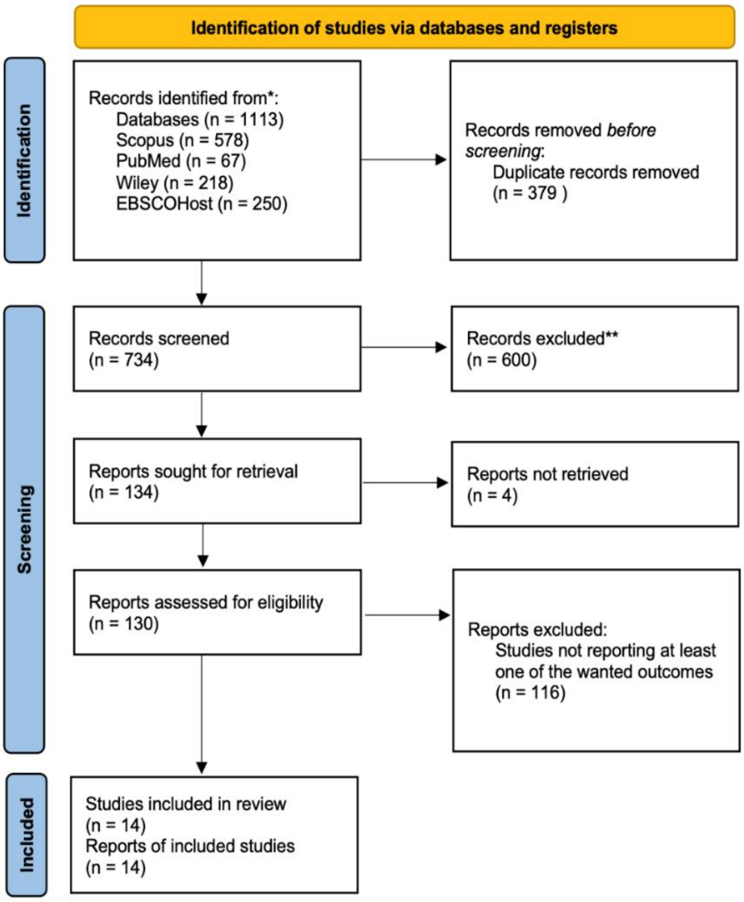


Figure 2. PRISMA diagram of the detailed process of studies selection

telerehabilitation (1 study), aerobic training with strength conditioning (1 study), aerobic training with strength conditioning and telerehabilitation (1 study), aerobic training with strength conditioning, respiratory neuroplasticity training, and telerehabilitation (1 study), and telerehabilitation (3 studies). Comparators included sham procedures, treatment as usual, wait-list controls, or no treatment. The mean follow-up period across trials ranged from 4 to 12 weeks.

Meanwhile, among the 14 baseline studies on demographic characteristics, several trials reported incomplete or unspecified data: one did not clearly state baseline age (Pardo et al., 2023), while others lacked detailed reporting on disease duration or presented heterogeneous assessment measures. Complete study characteristics are shown in Supplementary Data 2.

Type of Intervention

A total of seven different interventions were reported (in the included studies) that were collated into the following seven categories: aerobic training (AT; n = 3), strength conditioning (SC; n = 1), telerehabilitation (TR; n = 2), neuromodulatory brain stimulation (NBS; n = 1), respiratory neuroplasticity training (RNT; n = 2), affective and cognitive integrations (ACI; n = 2), and usual care (UC; n = 4) (Table 2). Additionally, some studies used multimodal methods that included two or more categories (e.g., AT + SC; AT + SC + RNT; AT + TR). Table 2 presents detailed definitions of each intervention.

Table 2. Definition of each Intervention and Control

Intervention Category	Definition
Usual Care	No additional structured intervention beyond the participant's standard healthcare management. This may include treatment as usual provided by general practitioners, maintenance of daily activities, or follow-up within existing healthcare services.
Aerobic Training	Repetitive, rhythmic exercise engaging large muscle groups, prescribed to improve cardiorespiratory endurance. Typically delivered as treadmill walking, cycling, or equivalent at moderate-to-vigorous intensity (50–85% HRmax), 3–5 days/week.
Strength Conditioning	Structured resistance exercises aimed at improving muscle strength, endurance, and functional capacity. Usually performed with free weights, machines, or elastic bands, targeting major muscle groups 2–3 times/week.
Telerehabilitation	Delivery of rehabilitation services remotely through digital platforms (apps, video sessions, web-based modules), enabling supervision, education, and exercise prescription at a distance.
Neuromodulatory Brain Stimulation	Non-invasive brain stimulation techniques (e.g., transcranial direct current stimulation [tDCS], high definition tDCS, repetitive transcranial magnetic stimulation [rTMS]) used to modulate cortical excitability and promote neuroplasticity, targeting symptoms such as fatigue, cognition, and mood.
Respiratory Neuroplasticity Training	Training interventions such as inspiratory or expiratory muscle training (IMT/EMT) apply resistive or threshold loads to breathing muscles, enhancing respiratory strength and endurance, and promoting plasticity in ventilatory control.
Affective & Cognitive Integration	Mind-body interventions that integrate breathing retraining, mindfulness/meditation, guided imagery, sound/light therapy, or psychological wellbeing modules, aiming to reduce fatigue, improve mood, sleep, and cognitive performance.
Multimodal Combined Interventions (e.g., Aerobic Training + Strength Conditioning + Respiratory Neuroplasticity Training)	Programs integrating two or more modalities (aerobic, resistance, respiratory, or cognitive-affective training), designed to target multiple domains (cardiopulmonary fitness, muscular strength, respiratory function, and psychological wellbeing) simultaneously.

Quality Assessment of Included Studies

There are 14 studies included in which qualities are assessed using Cochrane ROB 2.0 results are presented in Figure 2. Most studies showed low risk in randomization process and selection of the reported result. While the latter domains might demonstrate a higher risk of bias.

The design of studies that focus on psychological therapies would raise concerns to deviations from the intended intervention due to the nature of it being difficult to blind both participants and personnels. This can escalate subjective outcomes in the findings caused by expectancy and placebo effects. Similarly, measurement of the outcome would also exhibit high concerns. Considering that most of the studies are not blinded and share the same limitations that stem from this condition. Taken together, these issues limit the validity of the evidence.

Missing outcome data also takes contribution in the rise of concerns. Dropouts are influenced by the severe fatigue and mental health issues coming from Long COVID, while some studies lack transparency of the missing data. These issues would lessen the reliability of the results.

All studies have also undergone GRADE analysis which revealed the findings' certainty and is presented in Supplementary 9, the results range from very low to high certainty. Affective and

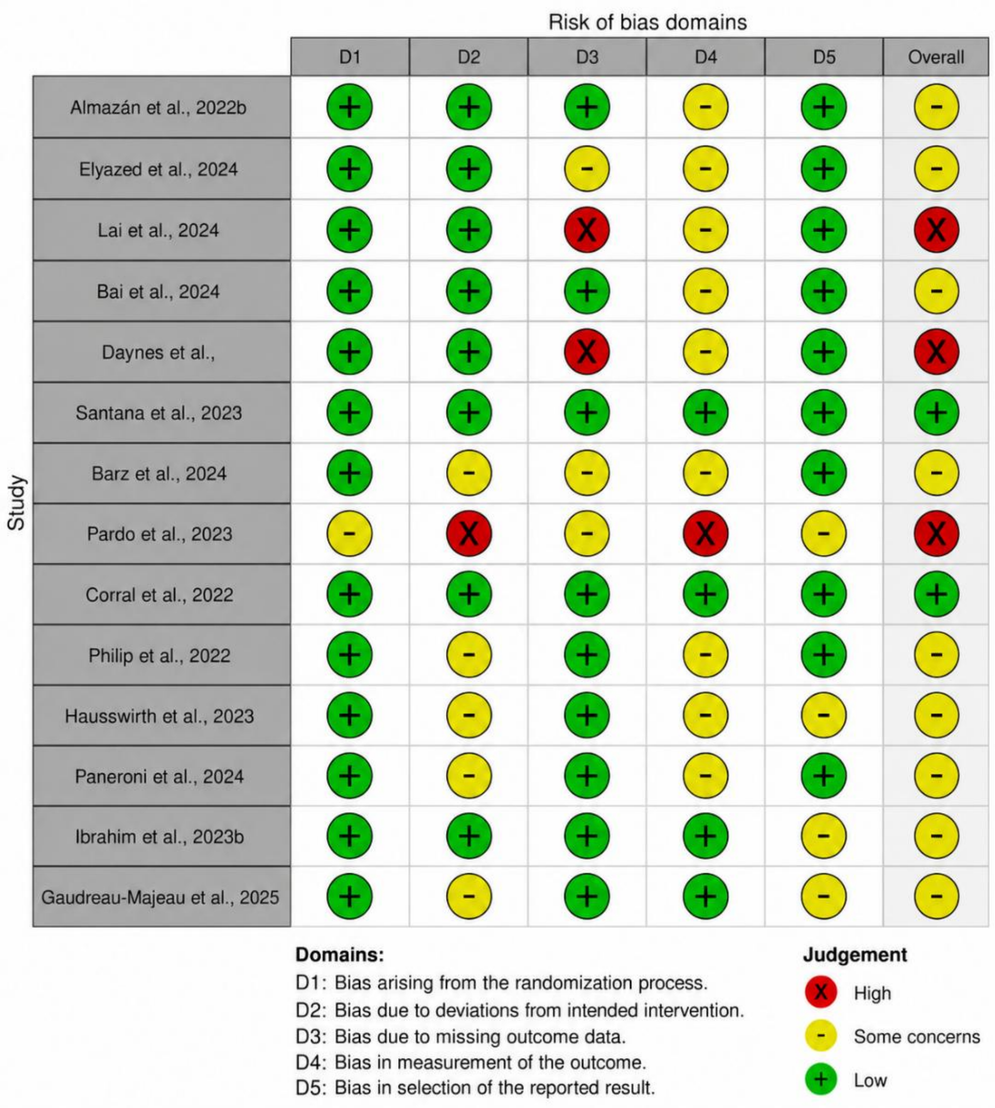


Figure 2. Risk of Bias of Included Studies

Cognitive Integration consistently serves high certainty compared to other interventions. This highlights the potential of psychological interventions in reducing fatigue burden in long COVID patients.

Moving to quality of life, here is seen that combining aerobic training, strength conditioning, respiratory neuroplasticity training, and telerehabilitation showed significant improvement, supported by high certainty and network evidence. Multimodal neurorehabilitation approaches demonstrate the importance of integrated interventions over single-modality therapies.

While seemingly fatigue and quality of life have found their light, studies researching the effect of psychological interventions towards mental health have displayed more profound uncertainty. The wide variety of neurotherapies showed no significant benefit over usual care, limited by inconsistent results across trials, potential publication bias, and low-to-moderate certainty evidence. The effectiveness of neurotherapies to improve mental health would be claimed to stay inconclusive.

In conclusion, these findings suggest credible certainty of neurotherapies in improving fatigue and quality of life in long COVID patients, even though their role in mental health recovery remains uncertain. The results of the risk of bias assessment indicate that this review should be interpreted with caution. Missing outcome data, relying to self-reported measure, and the lack of blinding coming from the nature of the studies' design might inflate subjective outcomes, therefore adding as a source to uncertainty of the effect estimates.

Studies Included in Network Meta-Analysis

Each node represents an intervention tested in clinical trials, with node size proportional to the number of patients receiving the intervention and line thickness representing the number of trials comparing the interventions. In Figure 3 (A) Fatigue Severity Outcome, the network includes multiple interventions: "Aerobic Exercise Training," "Strength Conditioning," "Breathing Training," "Cognitive Behavioral Training," "Neuromodulatory Brain Stimulation," "Telerehabilitation," and their combinations, with "Usual Care" as a reference.

Whereas, Figure 3 (B) Mental Health Outcome consists of "Aerobic Exercise Training," "Strength Conditioning," "Breathing Training," "Cognitive Behavioral Training," "Neuromodulatory Braing Stimulation," "Telerehabilitation," and their combinations, with "Usual Care" as a reference and forming a balanced network and predominantly driven by cognitive behavioral therapy and exercise-based approaches.

Lastly, Figure 3 (C) Quality of Life Outcome shows the same type of interventions, with a dominance of exercise interventions (including strength conditioning and breathing training) that are interconnected with various other approaches, although not all interventions are directly connected to one another.

Effects of Interventions on Fatigue Outcome

The network structure for fatigue severity was fairly well connected as most interventions were able to be compared directly or indirectly to usual care (shown in the netgraph, Figure 4A). Affective and Cognitive Integration produced the largest reduction in fatigue severity compared to usual care (SMD = −5.01, 95% CI −6.38 to −3.65) with significant benefits also identified for Neuromodulatory Brain Stimulation (SMD = −1.33, 95% CI −1.84 to −0.81), Aerobic Training with Strength Conditioning (SMD = −1.03, 95% CI −1.33 to −0.72), and the multimodal program with aerobic, strength, respiratory, and telerehabilitation components (SMD = −1.45, 95% CI −2.02 to −0.88). By contrast, the Aerobic Training program, the Aerobic Training plus Telerehabilitation program, and the Affective and Cognitive Integration plus Telerehabilitation program did not show a statistically significant difference when compared to usual care (Figure 4A).

These findings was further supported by our treatment rankings (Figure 5A), indicating that Affective and Cognitive Integration had the highest probability of being the best intervention for participants (SUCRA ≈ 90%), followed by the multimodal program and Aerobic + Strength Conditioning, Finally, Aerobic Training and its combinations with telerehabilitation ranked lowest for priority, being close to usual care.

Further evaluation of the network provided evidence for validity, no heterogeneity ($\tau^2 = 0$, $I^2 = 0\%$, Supplementary Data 6) and no inconsistency was found (all $p > 0.05$) between direct and indirect estimates (Supplementary Data 7.1). The contribution matrix (Supplementary Data 5.1) suggested that direct evidence mainly stemmed from aerobic and strength-based vs usual care interventions, whereas Affective and Cognitive Integration was largely influenced by indirect evidence. The comparison-corrected funnel plot was symmetrical and indicated little to no risk of reporting bias (Supplementary Data 8.1). Finally, the Affective and Cognitive Integration overall assessment of GRADE analysis showed high certainty, which further strengthen the confident of the result (Supplementary Data 9.1).

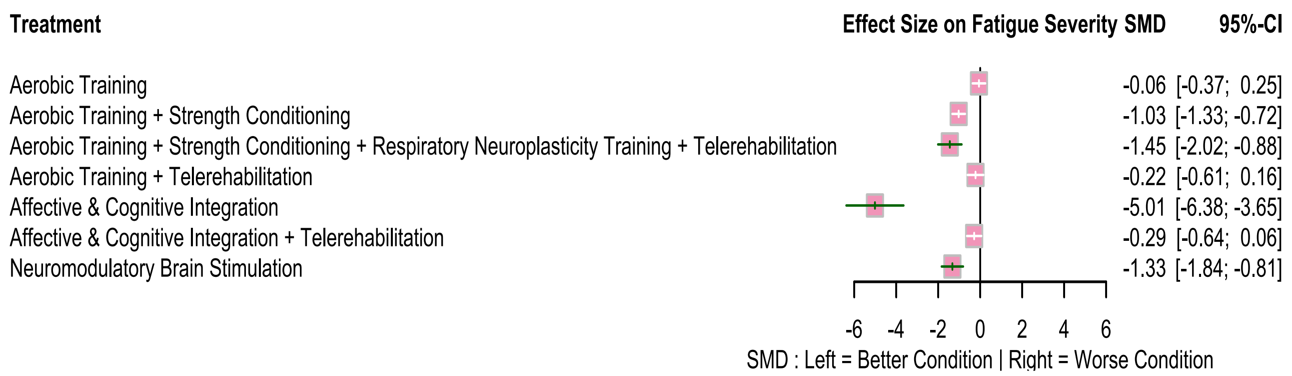
Effects of Interventions on Mental Health Outcome

Similar to fatigue, the network for mental health severity was well connected, with most interventions linked to usual care (netgraph, Figure 3B). However, in contrast to the certainty findings for fatigue, the estimations for mental health included a great deal of uncertainty. None of the interventions indicated statistically significant benefits compared to usual care, evidenced by wide confidence intervals that crossed the null (Figure 4B). As examples, Aerobic Training (SMD= –0.99, 95% CI –2.42 to 0.45), Affective and Cognitive Integration method (SMD = –0.81, 95% CI –3.30 to 1.68), or Neuromodulatory Brain Stimulation (SMD = –1.15, 95% CI –3.60 to 1.29) did not show clear effects.

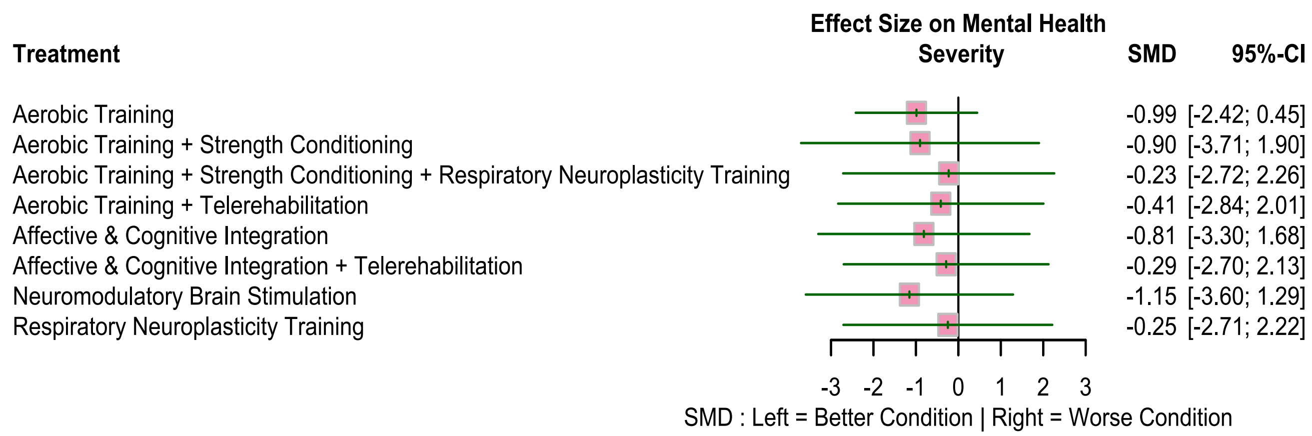
Figure 3. Network graph across all interventions assessed using A) Fatigue Severity Outcome, B) Mental Health Outcome, and C) Quality of Life Outcome

Network Meta-Analysis Results for Outcomes

A) Fatigue Severity Symptom



B) Mental Health Severity Outcome



C) Quality of Life Outcome

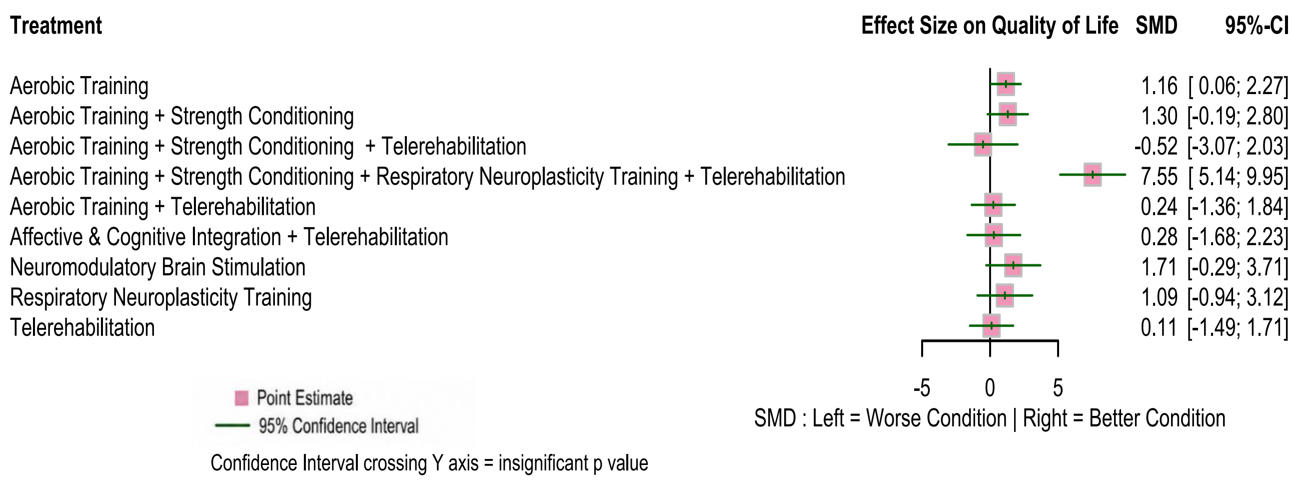
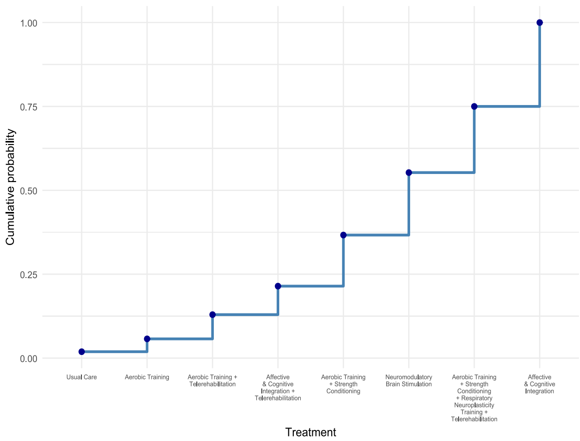
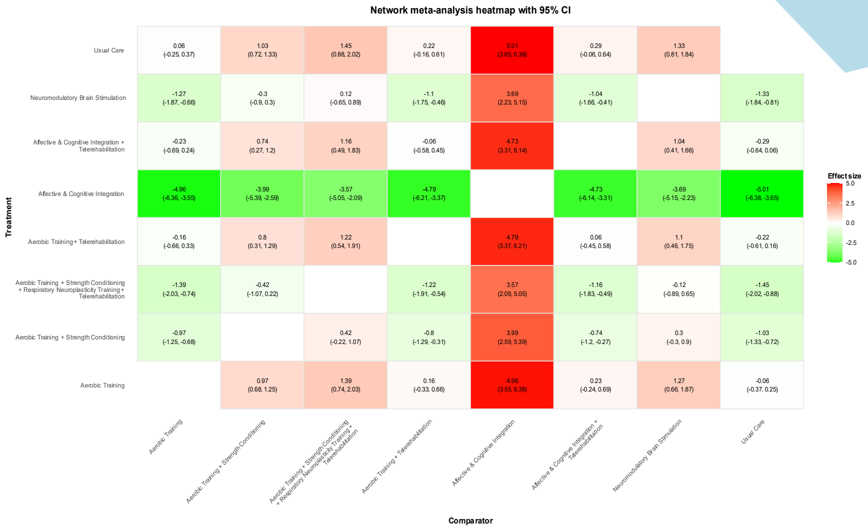


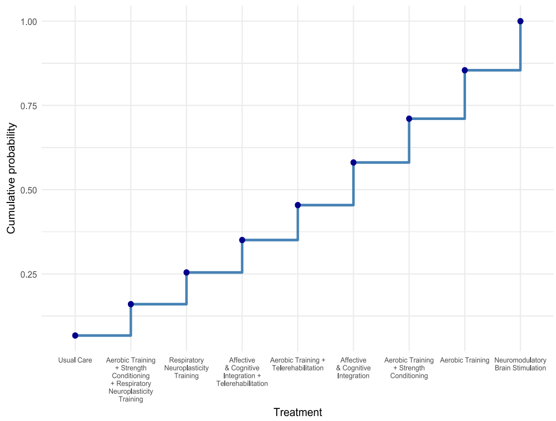
Figure 4. Network Meta-Analysis Result of Interventions across All Outcomes

A) Fatigue Severity Symptom

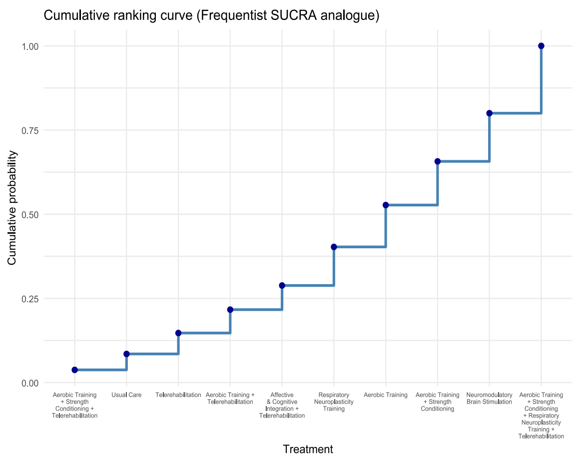




B) Mental Health Severity Outcome



C) Quality of Life Outcome



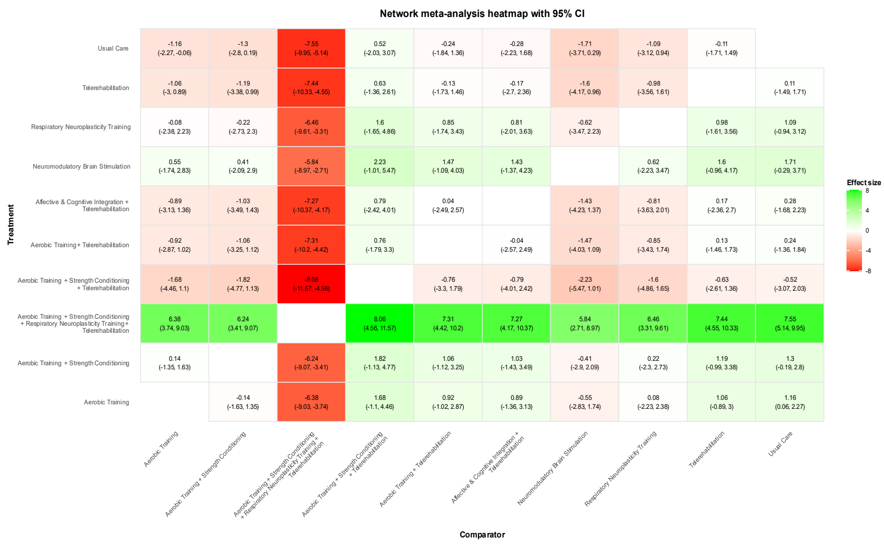


Figure 5. Treatment rankings and heatmaps for three outcomes. (See main text for details.)

Treatment ranking probabilities (shown in SUCRA, Figure 4B) favored Neuromodulatory Brain Stimulation and Aerobic Training, while Respiratory Neuroplasticity Training and multimodal program ranked lower. However, treatment rank probabilities should be viewed cautiously due to the absence of significant pairwise effects (shown in netheat, Figure 5B).

We found substantial heterogeneity in assessment of assumptions of the models (τ^2 = 1.220, I^2 = 93.4%), and moderate evidence of inconsistency (Q = 30.262, df = 2, $p < 0.001$) limiting our confidence in these estimates (Supplementary Data 6). There was also some possible publication bias, as both the original and adjusted comparison-corrected funnel plots were still asymmetric and provided evidence of small-study effects (Supplementary Data 8.2).

Given these possible implications, we concluded that the literature's certainty of evidence overall was low to moderate (Supplementary Data 9.2). Aerobic Training and Aerobic Training + Telerehabilitation had low certainty because of risk of bias and imprecision. Aerobic Training + Strength Conditioning had a very low certainty judgement due to inconsistency. Neuromodulatory Brain Stimulation, Affective and Cognitive Integration, and Respiratory Neuroplasticity Training all had moderate certainty judgement. Overall, these considerations indicate that while some interventions exhibit promise, the overall strength of evidence for mental health outcomes in long COVID is limited.

Effects of Interventions on Quality of Life Outcome

The network for quality of life was comprised of 10 interventions (Figure 3C) all directly or indirectly connected to usual care. The multimodal program (Aerobic training + strength conditioning + respiratory neuroplasticity + telerehabilitation) produced the largest effect size for quality of life (SMD = 7.55, 95% CI 5.14 to 9.95). Aerobic training also had an effect size that was statistically significant although smaller (SMD = 1.16, 95% CI 0.06 to 2.27). However, other combinations did not have any significant differences from usual care, such as Aerobic + Strength conditioning, Aerobic + Telerehabilitation, Affective and Cognitive Integration + Telerehabilitation, Neuromodulatory Brain Stimulation, Respiratory Neuroplasticity Training, and Telerehabilitation alone (Figure 4C).

The treatment rankings (Figure 5C) further confirmed that the multimodal intervention was superior, followed by aerobic training, aerobic + strength conditioning and usual care, telerehabilitation alone and Affective and Cognitive Integration + Telerehabilitation consistently had the lowest ranking.

Nevertheless, caution must be done in interpreting the above findings. We observed significant heterogeneity (τ^2 = 0.983, I^2 = 94.6%) and considerable inconsistency (Q = 73.512, df = 4, $p < 0.001$), indicating significant variation and disagreement between our direct and indirect evidence (Supplementary Data 6). We also noted possible publication bias with respect to heterogeneity in our funnel plot assessment (both original and adjusted) showing persistent asymmetry (Supplementary Data 8.3).

Moreover, certainty of evidence differed across interventions (Supplementary Data 9.3). The multimodal program and Respiratory Neuroplasticity Training interventions were rated high certainty; thus, we have confidence in their effects. The Neuromodulatory Brain Stimulation, Affective and Cognitive Integration + Telerehabilitation, and Aerobic + Strength Conditioning were rated moderate certainty, while Aerobic Training and Aerobic + Telerehabilitation were rated low certainty. Aerobic + Strength Conditioning + Telerehabilitation was rated at very low certainty. Overall, while the multimodal program demonstrated the greatest potential benefit, the high heterogeneity and possible publication bias means caution interpretation.

Discussion

Summary of findings

This systematic review and network meta-analysis synthesized evidence from 14 randomized controlled trials evaluating neurotherapies for Long COVID, focusing on fatigue, mental health, and quality of life outcomes. The findings suggest that affective and cognitive integration may improve fatigue severity, while multimodal interventions appear to provide the greatest benefit for quality-of-life outcomes. In contrast, the effects of neurotherapies on mental health outcomes remain inconsistent across studies. Based on GRADE assessment, the certainty of evidence was strongest for fatigue severity, whereas the remaining outcomes demonstrated lower certainty levels.

The inclusion of multiple intervention categories in this review was intentional and aligned with the purpose of network meta-analysis, which enables comparisons across several competing interventions through both direct and indirect evidence synthesis. All included approaches were only non-pharmacological in nature, encompassing rehabilitation, neuromodulatory, respiratory, cognitive-affective, exercise-based, and multimodal strategies. This broad therapeutic approach is clinically relevant because Long COVID is characterized by complex and overlapping symptoms, including fatigue, shortness of breath, cognitive dysfunction, and mood disturbances, all of which substantially impair daily functioning and quality of life [1]. Current evidence suggests that these manifestations may involve neuroinflammation, blood–brain barrier disruption, and central nervous system involvement, making the condition difficult to address using single-target interventions alone [14,15]. Furthermore, because there are currently no FDA-approved therapies specifically targeting neurological manifestations of Long COVID, management primarily relies on symptomatic treatment and multidisciplinary rehabilitation strategies [16,17].

Interpretation of these findings should also consider considerable clinical and methodological heterogeneity across the included randomized controlled trials. The interventions differed substantially in therapeutic approach, treatment intensity, duration, frequency, and mode of delivery, while fatigue, quality of life, and mental health were assessed using different validated outcome instruments across studies. Although standardized mean differences enabled pooling across different measurement scales, differences in the clinical domains captured by these instruments may have contributed to the substantial statistical heterogeneity observed, particularly for quality-of-life and mental health outcomes.

Effectiveness of Affective and Cognitive Integration

In the human body, SARS-CoV-2 can reach the central nervous system (CNS) through several mechanisms. One pathway is through the nasal cavity, where the virus binds to the olfactory epithelium via the ACE-2 receptors. The virus then invades the olfactory nerves and travels along the olfactory tract to the brainstem[18]. SARS-CoV-2 could also directly damage the brain by permeating the blood-brain barrier (BBB) and spreading the virus into the central nervous system, which may explain the neurological symptoms of long COVID[19]. Prolonged inflammation in the brain causes a significant increase in cytokines, especially IL-6.

In this study, Affective and Cognitive Integration includes mind-body interventions such as breathing retraining and meditation. In this case, guided breathing techniques may help physical and mental fatigue by restoring autonomic nervous system balance, optimizing oxygen delivery, and lowering stress levels. While meditation, particularly the aspect of mindfulness, reduces fatigue by lowering inflammatory effects of infection. A meta-analysis by Jiang in 2021 shows that mindfulness meditation shows effectiveness in improving immune markers in people with AIDS[20]. Another meta-analysis by Sanada shows that mindfulness-based intervention may lead to lower-grade inflammation[21]. To add to that, meditation has been shown to influence gene expression related to chromatin regulation and inflammatory processes, including the downregulation of the tumor necrosis factor (TNF) pathway[22]. It is also associated with reductions in stress, anxiety, and pro-inflammatory cytokines such as IL-6 and IL-8, while promoting an increase in anti-inflammatory cytokines like IL-10[23]. These findings show that meditation has positively been associated with better inflammatory process changes. In summary, symptoms of inflammatory-driven pathogenesis of virulent disease, like fatigue, can be modified by the anti-inflammatory properties of meditation.

It should be noted, however, that the trials grouped under affective and cognitive integration differed in their specific protocols, including the type of meditation, breathing technique, session length, and the program duration. These heterogenous methods limit the ability to identify the precise intervention procedure that clinicians may want to take into practice. Adding up, the pooled effect should be interpreted as a category-level indication rather than reinforcing a single standardized protocol.

Effectiveness of Neurotherapies on Mental Health

Unlike fatigue and quality-of-life outcomes, neurotherapies did not demonstrate consistent improvements in mental health. This finding is biologically plausible because psychological recovery in Long COVID is influenced by multiple interacting mechanisms beyond physical impairment alone. Persistent neuroinflammation, autonomic dysfunction, sleep disturbance, uncertainty regarding recovery, reduced social participation, and prolonged functional limitations may all contribute to anxiety, depression, and psychological distress [38, 39]. Consequently, interventions primarily targeting physical rehabilitation may not necessarily produce equivalent improvements in psychological outcomes, particularly over relatively short intervention periods.

Methodological variability may have further contributed to the uncertainty of mental health findings. Although all included trials evaluated mental health, they measured different psychological constructs using different validated instruments. Some studies primarily assessed anxiety and depression, whereas others focused on perceived stress, mood disturbance, or broader psychological well-being. Consequently, the pooled analysis combined related but non-identical psychological outcomes. Although standardized mean differences enabled quantitative synthesis across different measurement scales, they cannot fully account for conceptual differences between these instruments, which likely contributed to the substantial heterogeneity and inconsistent treatment effects observed across studies.

Effectiveness of Multimodal Intervention

Multimodal intervention combines aerobic training, strength conditioning, respiratory neuroplasticity training, and telerehabilitation. It demonstrated the most consistent effect in the quality-of-life domain. Aerobic training involves repetitive, rhythmic exercise that engages large muscle groups which enhances cardiovascular fitness. It's usually delivered as treadmill, waking or cycling 3—5 times a week. In COVID, the virus SARS-CoV-2 infects the central nervous system while invading skeletal muscles and neuromuscular junctions. Aerobic training may help with these issues through the integrated effects of larger and more fused mitochondrial network in the skeletal muscle, as well as beneficial effects on the cardiorespiratory system, central nervous system, and peripheral muscle fiber repair[24, 25]. In the context of Long COVID, exercise interventions can help relieve fatigue, chest pain, and cognitive impairment[26]. By increasing aerobic capacity, patients experience less persistent fatigue, greater exercise tolerance, and improved ability to perform daily activities without excessive exhaustion[27].

Strength conditioning exercises aim at improving muscle strength, endurance, and functional capacity. It involves exercises that target major muscle groups with the use of free weight, machines, or elastic bands. It is beneficial as Long COVID has been found to negatively impact multiple organs, including skeletal muscle. This is crucial as muscles play a vital role in movement, maintaining balance and posture, supporting daily activities, and even regulating various metabolic functions. Patients with Long COVID tend to experience muscle loss and weakness because of prolonged inactivity and ongoing systemic inflammation. Persistent systemic inflammation is sustained by increased levels of interferon gamma, C-reactive protein, IL-6, IL-2, IL-10, and tumor necrosis factor-α[30, 31]. These proinflammatory cytokines are known to disrupt muscle protein metabolism[35]. This is where strength conditioning intervenes by targeting the recovery of muscle mass and power which benefits both the peripheral and respiratory muscles, supporting mobility, and efficient breathing. Greater muscle strength reduces fatigue, improves balance, and mobility. Another major benefit is that it trains musculoskeletal comfort, which promotes independence and overall physical function[31].

Respiratory neuroplasticity training focuses on retraining weakened respiratory muscles, especially due to COVID-19 infection. It involves interventions such as inspiratory or expiratory muscle training which enhances respiratory strength and endurance, promoting plasticity in ventilatory control. This training promotes respiratory muscle strength and reduces dyspnea[32]. A systematic review and meta-analysis proved that pulmonary rehabilitation programs combining respiratory muscle training with aerobic and resistance exercise show reduces fatigue and better physiological condition, which are important in Long COVID recovery[33].

Telerehabilitation means the delivery of rehabilitation services through a digital platform. It offers remote supervision and individualized programs that remain accessible at all times, especially during infection-related risks or for patients with limited mobility. Home-based telerehabilitation has been demonstrated to safely enhance exercise capacity, muscle strength, and endurance in post-COVID-19 patients[34]. Telerehabilitation enables continuous monitoring and adjustment of the intervention to reduce worsening of the clinical condition[35].

Overall, quality of life (QoL) is influenced by multiple interrelated aspects of physical health, psychological, social relationships, and environment. A single or stand-alone intervention often targets only one domain. While it may yield some benefits, its overall impact on improving one's quality of life remains limited. In contrast, a multimodal approach that integrates aerobic training, strength conditioning, respiratory neuroplasticity training, and telerehabilitation offers a more comprehensive recovery strategy. This holistic combination addresses both neurocognitive and non-neurological dimensions in Long COVID symptoms, which explains why multimodal interventions demonstrate superior improvements in QoL score compared to single interventions. On the other hand, these interventions do not show equally consistent effects in the mental health domain. Symptoms such as anxiety, depression, brain fog, and persistent fatigue in Long COVID are shaped by a complex interplay of biological factors, psychological stress, and social determinants, which explain why it is difficult to address through exercise-based or physical rehabilitation alone[36].

The interpretation of these findings should also consider the methodological variability of the included studies. Although all trials evaluated health-related quality of life, different validated instruments were used, each emphasizing different combinations of physical, psychological, social, and functional domains. Consequently, the pooled effect represents an overall improvement in health-related quality of life rather than a specific QoL dimension. While standardized mean differences enabled quantitative synthesis across these instruments, conceptual differences between outcome measures may have contributed to the substantial heterogeneity observed for this outcome.

Thus, the results of this study must be cautiously interpreted. The multimodal interventions analyzed in this review encompassed a broad range of intervention combinations rather than a single standardized protocol that can be readily replicated across settings. Such variability complicates the interpretation of pooled effects within a network meta-analysis framework, meaning that the observed superiority should not be regarded as definitive evidence of efficacy. Nevertheless, the result is biologically plausible due to the multidimensional character of the impact of Long COVID on quality of life. However, since the studies did not use the component-level approach, the role of each component in the resulting pooled result is unknown.

Strength, Limitation, & Future Directions

A major strength of this review is the comprehensive evaluation of diverse neurotherapies using network meta-analysis, allowing comparison across multiple interventions even in the absence of head-to-head randomized controlled trials. The findings were further strengthened by GRADE for certainty assessments, providing a transparent evaluation of confidence in the evidence. Consequently, this review offers symptom-specific rehabilitation recommendations that may assist clinicians in tailoring individualized non-pharmacological interventions, particularly for reducing fatigue and improving quality of life.

Nevertheless, several limitations should be considered. First, this review was not prospectively registered, which may reduce methodological transparency and increase the risk of selective reporting bias. Previous studies have emphasized that protocol registration enhances transparency, minimizes reporting bias, and prevents unnecessary duplication of systematic reviews. Therefore, the absence of protocol registration should be considered when interpreting the findings. Second, the overall certainty of the conclusions was limited by the absence of significant findings for mental health outcomes and by the substantial clinical and methodological heterogeneity across the included randomized controlled trials. The interventions differed considerably in therapeutic approach, treatment intensity, duration, frequency, and mode of delivery. Furthermore, fatigue, quality of life, and mental health were assessed using different validated instruments across studies, including the Modified Fatigue Impact Scale (MFIS), Fatigue Severity Scale (FSS), and Chalder Fatigue Scale for fatigue; the SF-36, SF-12, RAND-36, EQ-5D, and WHOQOL-BREF for quality of life; and the Hospital Anxiety and Depression Scale

(HADS), Hamilton Anxiety and Depression Rating Scales (HAM-A/HAM-D), Perceived Stress Scale (PSS), and Profile of Mood States (POMS) for mental health. Although standardized mean differences enabled quantitative synthesis across different measurement scales, these instruments assess related but not identical constructs and therefore cannot eliminate conceptual heterogeneity, which likely contributed to the substantial statistical heterogeneity observed, particularly for quality-of-life and mental health outcomes. In addition, reliance on self-reported outcome measures may have introduced reporting bias and reduced the reliability of the pooled estimates. Several included studies also did not adequately report whether participants switched, combined, or modified non-pharmacological therapies during follow-up, making it difficult to evaluate the influence of treatment changes over time. Moreover, variations in intervention implementation may have weakened the transitivity assumption and reduced the robustness of inconsistency assessments, particularly because several network comparisons were informed by only a limited number of trials.

To strengthen the evidence base, future randomized controlled trials should adopt more standardized intervention protocols and harmonized outcome assessment instruments to improve comparability across studies and reduce clinical and methodological heterogeneity. Standardizing validated measures for fatigue, quality of life, and mental health would facilitate more robust quantitative synthesis and improve the interpretability of future network meta-analyses. Longer follow-up periods are also warranted, particularly to determine whether neurorehabilitation produces sustained improvements in psychological outcomes, which may require longer recovery trajectories than physical symptoms. Furthermore, future studies should comprehensively report intervention modifications, treatment switching, adherence, and concurrent therapies throughout follow-up to strengthen transitivity assumptions and improve the validity of indirect comparisons. Finally, adequately powered multicenter randomized controlled trials are needed to provide stronger evidence for comparative effectiveness across different neurorehabilitation strategies. Overall, this review highlights the potential role of neurorehabilitation in reducing fatigue and improving quality of life among individuals with Long COVID while emphasizing the need for greater methodological standardization, particularly in studies evaluating mental health outcomes.

Conclusion

This systematic review and network meta-analysis present strong evidence for Affective and Cognitive Integration as the optimal neurotherapy for fatigue reduction in Long COVID, primarily through autonomic nervous system rebalancing, reduced pro-inflammatory cytokines, and modulation of stress response. Multimodal interventions consisting of aerobic training, strength conditioning, respiratory neuroplasticity training, and telerehabilitation consistently enhanced quality of life. Though mental health findings are less conclusive, the physiological trends suggest neuromodulation therapies and exercise-based therapies might modulate neuroinflammation and neuroplasticity, ultimately benefiting mood and cognition.

The major strength of this review lies in the application of network meta-analysis technique, enabling indirect comparisons across various forms of neurotherapies where direct evidence is absent. Findings should nonetheless be interpreted cautiously owing to the intervention mechanism of heterogeneity, small sample sizes, short follow-up durations, and reliance on patient-reported outcomes. Accordingly, the present findings should be regarded as a direction guide rather than being definitive. Overall, this review highlights promising research directions to develop individualized, evidence-informed neurotherapeutic rehabilitation protocols in Long COVID.

Conflict of Interest

The authors declared no conflict of interest.

Acknowledgment

The authors declared no acknowledgment.

Funding

No external funding was received.

Supplementary Materials

Supplementary materials related to this article are available from the corresponding author upon reasonable request.

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